

**DRAFT****PATENT**Attorney Docket No. **GENITOP-03849**

5. (Amended) The ~~multivalent vaccine~~ composition of Claim 1 further comprising at least one pharmaceutically acceptable excipient.

6. (Amended) The ~~multivalent vaccine~~ composition of Claim 1 further comprising an adjuvant.

7-24. (canceled)

25. (Amended) A ~~vaccine~~ composition for active idiotype immunotherapy produced according to a method comprising:

- a) providing:
  - i) malignant B cells isolated from a patient having a quasi-clonal B-cell lymphoma;
  - ii) an expression vector;
  - iii) an amplification vector comprising a recombinant oligonucleotide having a sequence encoding a first inhibitable enzyme operably linked to a heterologous promoter; and
  - iv) a T lymphoid parent cell line;
- b) isolating nucleic acid from said malignant cells, said nucleic acid comprising nucleotide sequences encoding at least one V<sub>H</sub> region and at least one V<sub>L</sub> region, said V<sub>H</sub> and V<sub>L</sub> regions derived from immunoglobulin molecules expressed by said malignant cells;
- c) inserting said nucleotide sequences encoding said V<sub>H</sub> and V<sub>L</sub> regions into said expression vector ;
- d) introducing said expression vector and said amplification vector into said parent cell line to generate one or more transformed cells;
- e) growing said transformed cells in a first aqueous solution containing an inhibitor capable of inhibiting said first inhibitable enzyme wherein the concentration of said inhibitor present in said first aqueous solution is sufficient to prevent growth of said parent cell line; and

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f) identifying a transformed cell capable of growth in said first aqueous solution, wherein said transformed cell capable of growth expresses said V<sub>H</sub> and V<sub>L</sub> regions wherein V<sub>H</sub> and V<sub>L</sub> regions comprise a protein molecule useful as said ~~vaccine~~ active idiotype immunotherapy.

26. (Previously added) The composition of Claim 25, wherein nucleotide sequences encoding said V<sub>H</sub> and V<sub>L</sub> regions comprise at least two V<sub>H</sub> and at least one V<sub>L</sub> regions.

27. (Previously added) The composition of Claim 25, wherein nucleotide sequences encoding said V<sub>H</sub> and V<sub>L</sub> regions comprise at least one V<sub>H</sub> and at least two V<sub>L</sub> regions.

28. (Amended) A ~~vaccine~~ composition <sup>^</sup>for active idiotype immunotherapy<sup>^</sup> produced according to a method comprising:

- a) providing:
  - i) malignant B cells isolated from a patient having a quasi-clonal B-cell lymphoma;
  - ii) an expression vector;
  - iii) an amplification vector comprising a first recombinant oligonucleotide having a sequence encoding a first inhibitable enzyme operably linked to a heterologous promoter;
  - iv) a selection vector comprising a second recombinant oligonucleotide having a sequence which encodes a selectable gene product; and
  - v) a T lymphoid parent cell line;
- b) isolating nucleic acid from said malignant cells, said nucleic acid comprising nucleotide sequences encoding at least one V<sub>H</sub> region and at least one V<sub>L</sub> region, said V<sub>H</sub> and V<sub>L</sub> regions derived from immunoglobulin molecules expressed by said malignant cells;
- c) inserting said nucleotide sequences encoding said V<sub>H</sub> and V<sub>L</sub> regions into said expression vector;

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- d) introducing said expression vector, said amplification vector and said selection vector into said parent cell line to generate transformed cells;
- e) introducing said transformed cells into a first aqueous solution, said first aqueous solution requiring the expression of said selectable gene product for growth of said transformed cells;
- f) identifying at least one transformed cell capable of growth in said first aqueous solution;
- g) introducing said transformed cell capable of growth in said first aqueous medium into a second aqueous solution, said second aqueous solution comprising an inhibitor capable of inhibiting said first inhibitable enzyme, wherein the concentration of said inhibitor present in said second aqueous solution is sufficient to prevent growth of said parent cell line; and
- h) identifying at least one transformed cell capable of growth in said second aqueous solution, wherein said transformed cell capable of growth expresses said  $V_H$  and  $V_L$  regions wherein said  $V_H$  and  $V_L$  regions comprise a protein molecule.

29. (Amended) A ~~vaccine~~ composition for active idiotype immunotherapy produced according to a method comprising:

- a) providing:
  - i) malignant B cells isolated from a patient having a quasi-clonal B-cell lymphoma;
  - ii) an expression vector;
  - iii) an amplification vector comprising a first recombinant oligonucleotide having a sequence encoding a first inhibitable enzyme operably linked to a heterologous promoter;
  - iv) a selection vector comprising a second recombinant oligonucleotide having a sequence which encodes a selectable gene product; and
  - v) a T lymphoid parent cell line;

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- b) isolating nucleic acid from said malignant cells, said nucleic acid comprising nucleotide sequences encoding at least one V<sub>H</sub> region and at least one V<sub>L</sub> region, said V<sub>H</sub> and V<sub>L</sub> regions derived from immunoglobulin molecules expressed by said malignant cells;
- c) inserting said nucleotide sequences encoding said V<sub>H</sub> and V<sub>L</sub> regions into said expression vector;
- d) introducing said expression vector, said amplification vector and said selection vector into said parent cell line to generate transformed cells;
- e) introducing said transformed cells into a first aqueous solution, said first aqueous solution requiring the expression of said selectable gene product for growth of said transformed cells;
- f) identifying at least one individual clone of transformed cells capable of growth in said first aqueous solution;
- g) introducing said individual clone capable of growth in said first aqueous solution into a second aqueous solution, said second aqueous solution comprising an inhibitor capable of inhibiting said first inhibitable enzyme, wherein the concentration of said inhibitor present in said first aqueous solution is sufficient to prevent growth of said parent cell line; and
- h) identifying at least one individual clone capable of growth in said second aqueous solution, wherein said clone capable of growth expresses said V<sub>H</sub> and V<sub>L</sub> regions wherein said V<sub>H</sub> and V<sub>L</sub> regions comprise a protein molecule.

30. (Amended) A multivalent ~~vaccine~~-composition for active idiotype immunotherapy comprising at least two recombinant variable regions of immunoglobulin molecules derived from quasi-clonal B-cell lymphoma cells from a single patient, wherein said cells express at least two different immunoglobulin molecules, said immunoglobulin molecules differing by at least one idiotope, wherein said at least two recombinant variable regions of immunoglobulin molecules are derived by a method comprising the step of amplifying cDNA for said variable regions from mRNA from said B-cell lymphoma cells using amplification primers complementary to conserved sequences flanking said variable regions.